RECONSTRUCTION OF *Nannochloropsis oculata* PROTEIN-PROTEIN INTERACTION NETWORK FOR GROWTH AND TRIACYLGLYCEROL PRODUCTION

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SPECIALLY DEDICATED TO:

My *Abah*, Mahat bin Senon

My *Emak*, Habibah binti Hussein

My siblings:

Khamaliah, Kamaliana, Kamarudi, Kamisah dan Khairil Nizam

Brother and sister-in- laws:

Nazmi, Nur Hasanah, Mohd Zalman

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ABSTRACT

The aim of this study was to reconstruct protein-protein interaction map to allow researcher to identify pathway, biological roles and dynamic assembly of microalgae network pathways contributing to lipid production. The constructed PPI network was then characterised, and potential modifications were proposed based on this network to improve lipid production for mass biodiesel production. This bioinformatic approach is used to avoid the time consuming and expensive modification using high throughput approaches. In this study, literature search and data mining of rich information were interpreted into visualized outputs using Cystoscape. The outputs were then integrated and analysed to provide meaningful and reliable data. The study found that the constructed network consists of 153 nodes (proteins) and 1073 edges (interaction between proteins) with node degree R^2 coefficient distribution of 0.193 to exponent -0.387 denoting that the protein distributes randomly in the network and has clustering coefficient of 0.641 which was characterised by a highly connected node. The acyl-lipid (7-3)-desaturase (EDP09855) was identified as a bottleneck protein and a putative perturbation target for high quality biodiesel production. Cytoscape simulation and integration showed that alkaline growth conditions and phosphate and iron supplementation influenced PPI-directed pathway of *Chlamydomonas* sp. (model species) to glycerol lipid metabolism and fatty acid biosynthesis important for achieving high lipid productivity. In actual experimentation, microalgae *Nannochloropsis oculata* achieved highest percent of lipid yield when cultured in pH 8 growth conditions (3.45 %) or when growth was supplemented with 0.1 g/L phosphate (5.70 %) and 9.44 mg/L iron (6.21 %). Even though Cytoscape integration of three different vitamin B supplementation showed only minor possibility of pathway direction towards fatty acid biosynthesis in model species, maximum lipid productivity was achieved for *N. oculata* cultured using 500 µg/L biotin (4.98%), 50 µg/L thiamine (4.82%) and 0.5 µg/L cobalamin (7.59%). Altogether, computational biological pathway reconstruction positively supported network perturbations to optimize microalgae lipid productivity and actual experimentation validated the protein-protein network.

ABSTRAK

Tujuan kajian ini adalah untuk merangka semula peta interaksi protein-protein untuk membolehkan penyelidik mengenal pasti laluan, fungsi biologi dan rangkaian dinamik jejaring mikroalga yang menyumbang kepada pengeluaran lipid. Rangkaian PPI yang dibina kemudiannya dicirikan, dan pengubahsuaian yang berpotensi dicadangkan berdasarkan rangkaian ini untuk meningkatkan pengeluaran lipid bagi penghasilan biodiesel. Pendekatan bioinformatik ini digunakan untuk mengelakkan proses yang memakan masa yang lama dan kos yang tinggi dengan penggunaan pendekatan 'high throughput'. Dalam kajian ini, pencarian literatur dan perlombongan maklumat yang kaya ditafsirkan ke dalam hasil visual menggunakan 'Cystoscape'. Hasil ini kemudiannya diintegrasikan dan dianalisa untuk menghasilkan data yang bermakna dan boleh dipercayai. Kajian mendapati rangkaian yang dibina terdiri daripada 153 nod (protein) dan 1073 rangkaian (interaksi antara protein) dengan taburan koefisien darjah nod R^2 pada 0.193 hingga eksponen -0.387 menunjukkan bahawa protein tersusun secara rawak dalam rangkaian dan mempunyai pekali kluster 0.641 yang dicirikan oleh nod yang mempunyai hubungan tinggi. 'Acyl-lipid (7-3) -desaturase' (EDP09855) telah dikenal pasti sebagai protein cerutan dan sasaran pengubahsuaian untuk pengeluaran biodiesel yang berkualiti tinggi. Simulasi dan integrasi 'Cytoscape' menunjukkan bahawa keadaan pertumbuhan alkali dan suplemen fosfat dan zat besi mempengaruhi laluan yang diarahkan oleh PPI *Chlamydomonas* sp. (spesies model) ke metabolisme lipid gliserol dan biosintesis asid lemak yang penting untuk mencapai produktiviti lipid yang tinggi. Dalam eksperimen sebenar, mikroalga *Nannochloropsis oculata* mencapai peratusan tertinggi hasil lipid apabila dikulturkan dalam keadaan pertumbuhan pH 8 (3.45%) atau apabila pertumbuhan ditambah dengan 0.1 g/L fosfat (5.70%) dan 9.44 mg/L zat besi (6.21%). Walaupun integrasi 'Cytoscape' dari tiga jenis vitamin B yang berlainan menunjukkan hanya kemungkinan kecil arah jalur terarah ke biosintesis asid lemak dalam spesies model, produktiviti lipid maksimum *N. oculata* tercapai dengan menggunakan 500 μg/L biotin (4.98%), 50 μg/L tiamin (4.82%) dan 0.5 μg/L cobalamin (7.59%). Secara keseluruhannya, pembinaan semula laluan biologi komputasi menyokong pengubahsuaian rangkaian secara positif untuk mengoptimakan produktiviti lipid microalga dan eksperimen sebenar membuktikan rangkaian protein yang telah dibina adalah sah.

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LIST OF ABBREVIATIONS

PPI	-	Protein-protein interaction
KEGG	-	Kyoto Encyclopedia of Genes and Genomes
BLASTP	-	Basic Local Alignment Search Tool Protein
BLAST	-	Basic Local Alignment Search Tool
Tsv	-	Tab-separated values
DNA	-	deoxyribonucleic acid
UniProt	-	Universal Protein Knowledgebase
App	-	Application
API	-	Application programming interface
GO	-	Gene ontology
ATP	-	Adenosine triphosphate
NADPH	-	Nicotinamide adenine dinucleotide phosphate
RNA	-	Ribonucleic acid
FAME	-	Fatty acid methyl ester
TAG	-	Triacylglycerol
BC	-	Betweenness Centrality
CC	-	Closeness centrality
GC	-	Gas chromatography
CoA	-	Coenzyme A
ACP	-	Acyl carrier protein
DHAP	-	Dihydroxyacetone phosphate
GPAT	-	Glycerol-3-phosphate acyltransferase
PAP	-	Phosphatidic acid phosphatase

DAG	-	Diacylglycerol
LPAT	-	Lysophosphatidic acid acyl-transferase
DAGAT	-	Diacylglycerol acyltransferase
PDAT	-	Phospholipid: diacylglycerol transferase
TCA	-	Tricarboxylic acid
C	-	Carbon

LIST OF SYMBOLS

%	-	Percent
≥	-	Less than and equal to
≤	-	Higher than and equal to
<	-	Less than
>	-	Higher than
G	-	Gram
Mg	-	Milligram
L	-	Liter
g/L	-	Gram per liter
mg/L	-	Milligram per liter
µg/L	-	Microgram per liter
Ml	-	Milliliter
µM	-	Micrometer
v/v	-	Volume per volume
°C	-	Degree Celsius
Rpm	-	Rotation per minute
Ppt	-	Parts per thousand
R^2	-	R-squared
CO^2	-	Carbon dioxide
Ω	-	Omega
Vitamin B_1	-	Thiamine
Vitamin B_7	-	Biotin
Vitamin B_{12}	-	Cobalamin

$div.day^{-1}$	-	Division per day
div/day	-	Division per day

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CHAPTER 1

INTRODUCTION

1.1 Background information

The functions of proteins are complicated because there is a hierarchal order in which proteins work with each other to form all sorts of biological processes and pathways. Understanding protein–protein interaction (PPI) can ease the discovery of existing interactions in organism as it is crucial for the revelation of protein functions and pathways in biological processes (Zahiri *et al.*, 2013). Such understanding can be achieved by high throughput methods such as the yeast two-hybrid method (Xing *et al.*, 2016). The results from PPI analysis can provide predictions of undiscovered protein complexes, hence enhancing the understanding of the underlying principles of the organisms' cellular organisation and also predicting plausible functions of a protein in a particular biological pathway (King *et al.*, 2004). However, genomics- and proteomics-based experimental methods for protein–protein interaction studies are often expensive and tedious and can be plagued with uncertainties and problems in reproducibility (Zahiri *et al.*, 2013).

Direct experimental method approaches for optimisation of biodiesel production are unfeasible due to the complex regulatory network and mutual interaction of the physiological processes involved that require longer time to achieve desirable outcome (Rupprecht, 2009). As alternatives, several computational methods based on gene neighbourhood, gene fusion, phylogeny, docking, co-expression, and

interologs are developed to understand the protein–protein interaction, causing the recent rise of the systems biology discipline in the field of bioinformatics (Rupprecht, 2009). These computational methods have emerged as powerful platforms for protein–protein interaction network build-up, integration, and analysis that can also be employed to validate experimental results (Zahiri *et al.*, 2013). Other than that, the ability to obtain information over a wide range of study framework and information gathered across species based on conserved protein sequences (Shen *et al.*, 2007) facilitates the protein–protein interaction network build-up. Protein–protein interaction analysis can give insights on how to enhance high quality microalgae lipid production by understanding the rich information of the protein–protein interaction involved in specific pathways inside the microalgae (Blatti *et al.*, 2012) because the biological pathway reconstruction can be done through wide range of physical and functional interaction (Muley and Ranjan, 2013) with possible alteration over different growth parameter implementation during cultivation. In addition, the protein-protein interaction dynamics and assembly causing the interaction to be more specific and for instance, one enzyme might favour a specific outcome meanwhile interactions between the enzyme with different partner might change the protein activity (Cesa *et al.*, 2015). The protein–protein interaction network prediction is plausible but there is a lack of evidence on protein–protein interaction network study on microalgae, which increases the chances of getting false positive results. This problem can be resolved by the employment of gene ontology annotation (Mahdavi and Lin, 2007) that mark the biological process of each protein in the network to identify the targeted protein.

Microalgae are the most potential feedstock for biodiesel production as their oil can exceed 80% of the dry cell weight (Chisti, 2007). *Nannochloropsis oculata*, which belongs to the Eustigmatophyte group, has received so much attention because this species is rich with fatty acid and can achieve lipid content of up to 60% of dry cell weight (Doan *et al.*, 2011), topping the chart as the most reliable species for biodiesel production. *Nannochloropsis oculata* lipid constituents consist of mainly neutral lipids (Huang *et al.*, 2014) that can be readily converted into high quality biodiesel. Biodiesel from microalgae is produce by the transesterification of triacylglycerol (microalgae storage lipid) to produce fatty acid methyl ester

(FAME/biodiesel) (Mubarak *et al.*, 2015). High quality biodiesel is characterised by a high cetane number value which indicates that the biodiesel has high ignition quality (Knothe *et al.*, 2003). Cetane number increases as the degree of the fatty acid saturation decreases and the number of carbon increases, but the number of carbon needs to be kept low enough to avoid increase in viscosity that will lead to biodiesel deposition during cold temperatures (Knothe, 2005).Highly saturated fatty acids such as palmitic acid methyl ester, myristic acid methyl ester, stearic acid methyl ester, and undecanoic acid methyl ester are favoured components in biodiesel production as it will produce biodiesel with high cetane number (Rasoul-Amini *et al.*, 2011) thus this had shown that microalgae should produce lipid that contain saturated or mon-unsaturated fatty acid to ensure that the lipid being converted to fatty acid methyl ester (biodiesel) during transesterification is favourable lipid for high-quality biodiesel production.

Microalgae lipid content can be controlled by modifying certain aspects such as their growth conditions or nutrient requirements, which will result in the increase of triglyceride production (Goncalves *et al.*, 2016) for instance alkaline environment, iron (Huang *et al.*, 2014) and vitamins (Neumara *et al.*, 2014) supplementation during growth causes increased accumulation of neutral lipid mainly saturated and monounsaturated fatty acids. Since algae lipid is expressed as the percentage of dry cell weight of the starting material, microalgae growth rate needs to be taken into consideration as lipid productivity will increase as the microalgae biomass increases. Studies have shown that iron (Sasireka and Muthuvelayudham, 2015) and vitamin supplementation (Li-xin *et al.*, 2013) and alkaline conditions (Difusa *et al.*, 2015) play important roles in triggering the increase of microalgae biomass. Reconstruction of biological pathway through wide range of physical or functional protein-protein interaction network prediction were made possible nowadays (Muley and Ranjan, 2013). There is growing body of knowledge stated that protein-protein interaction network were able to highlight the importance of microalgae pathway reconstruction for accelerating the development of commercially viable biodiesel production from algae biomass (Blatti *et al.*, 2012).Therefore, this study attempts to enhance the mass productivity of high-quality biodiesel by manipulating microalgae growth aspects and lipid enhancing parameter in silico by reconstruction of the microalgae biological

pathway with the establishment of protein-protein interaction network prediction that will be further validated by laboratory-scale experiments. This research will extend our knowledge with two main strategies which are to increase the desired lipid per unit biomass and to increase the biomass density to maximise biomass per culture volume or area with the assistance of the established protein–protein interaction network reconstruction.

1.2 Problem statement

Since 1970, microalgae have been shown to be a promising third generation source for biodiesel production that can be sustainably developed (John S. *et al.*, 1998). However, a lot of studies still need to be conducted to optimise the production of high-quality biodiesel to meet the global demand on energy consumption. The understanding of all cellular processes is possible with protein–protein interaction but understanding the protein–protein interaction by high-throughput methods is time consuming and far from being cost effective (Raman, 2010). Thus, in this study, the protein–protein interaction networks were reconstructed by using bioinformatics techniques since they are more economical, rapid, and convenient as proven by the study conducted by Han *et al.* (Han *et al*., 2016). These in silico analyses provide data to help us understand the pathways involved in the growth and lipid production of microalgae so that these pathways can be targeted for modifications to enhance the microalgae growth and lipid production. As there is lack of experimental evidence to confirm the microalgae network reconstruction, the gene ontology annotation was employed to overcome the problem with the false positive outcomes (Ji et al., 2014).

1.3 Objectives

The objectives of this study are:

1. To mine and map protein–protein interaction network based on microalgae growth and triacylglycerol production and find the important node for putative perturbation target.

2. To identify the role of selected parameters in enhancing microalgae growth and triacylglycerol productivity through the established subnetwork.

3. To enhance the growth and microalgae triacylglycerol production and validate the established subnetwork through experimentation.

1.4 Scope of study

The study scope comprised the generation of candidate pathway of the network reconstruction in which various data sources were pooled together by using efficient text mining and literature mining procedure (Zahiri *et al.*, 2013) with the aid of tools such as Cytoscape plugins and open source databases. The data were then compiled, curated and filtered by using the STRING database (string-db.org) combined score (Szklarczyk *et al.*, 2017). The created protein–protein interaction network was visualised and integrated by using Cytoscape. The predicted protein–protein interaction network provide insight on the parameters for optimisation of *Nannochloropsis oculata* high quality biodiesel production. *Nannochloropsis oculata* was cultured under different growth parameter. Microalgae lipid was extracted and converted to biodiesel. Fatty acid profile was characterised by using gas chromatography.

1.5 Significances of study

This study was carried out to promote microalgae growth and lipid productivity in which the protein-protein interaction map had reveals the possible protein interaction and major molecular functions association of genes involve in microalgae growth and triacyglycerol production. This study facilitates the optimization of microalgae growth and lipid productivity based on the reconstruction of biological pathway in the protein-protein interaction network with alteration on the pH of growth environment and nutrient supplementation such as iron, phosphate, biotin, thiamin and cobalamin supplementation on the microalgae growth media. This study indicates the feasibility of using protein–protein interaction network to reconstruct the biological pathway and guides specific experiments for researcher.

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